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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/445,375	KINGSMAN ET AL.
	Examiner	Art Unit
	J. Eric Angell	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-118* is/are pending in the application.

4a) Of the above claim(s) *107-111* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-106 and 112-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

1. This Action is in response to the communication filed on 6/3/02, as Paper No. 25. The amendment has been entered. Claims 1-74 have been cancelled. New claims 75-118 have been added. Claims 75-118 are currently pending in the application and are addressed herein.

2. Applicant's arguments, as they apply to rejections of the new claims, are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Restriction is required under 35 U.S.C. 121 and 372.

Newly submitted claims 107-111 are directed to an invention which is not linked to the other claims as to form a single general inventive concept under PCT Rule 13.1.

The Groups of claims which form a single general inventive concept are as follows:

Group I, claim(s) claims 75-106 and 112-118, drawn to a vector and a method of treating cancer by directly delivering the vector to a tumor.

Group II, claim(s) 107-111, drawn to a method for expressing a polynucleotide sequence in a mammalian cell culture, and recovering the polynucleotide sequence from the mammalian culture.

4. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking the claims of Group I is a method of treating cancer using the vector of claim 75. The method of Group II is drawn to a method of treating cancer, but rather to a method of expressing and recovering a polynucleotide from a mammalian cell culture. Therefore, there is no special technical feature linking Groups I and II and restriction is proper. Furthermore, in determining unity of invention, a single general

inventive concept is viewed by the Office as one product one method of making and one method of using the product. In the instant case the product (a vector) and the method of treating cancer (one method of using the vector) constitute a single general inventive concept. The method of expressing the polynucleotide in a mammalian culture system does not relate to a method for treating cancer; therefore, it is a different method of using the vector, which constitutes a second (and separate) general inventive concept. Therefore, the restriction is appropriate.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim107-11 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 99 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 99 is indefinite because it recites the phrase, "comprising delivering directly to the tumor cells transduced *ex vivo*..." (Emphasis added for clarity). This phrase renders the claim indefinite because there is no antecedent basis for the "said tumor cells" in the claim.

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 75-83, 85-96, 98-100, 112-118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 96/30504) in view of Myers et al. (JBC Vol. 269, No. 12: p. 9319-9324; 1994) for the reasons of record, summarized below.

Anderson teaches a retroviral vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor interacting protein is targeted to a specific tumor cell type, and delivers a therapeutic product encode by a second polynucleotide of interest to the interior of the tumor cell (e.g., see abstract; p. 1, paragraphs 1-2; p. 19, second paragraph; and paragraph bridging p. 20-21); wherein the second polynucleotide of interest encodes a cytokine such as Tumor Necrosis Factors, Interferons, and Interleukins, (p. 21, second paragraph, and p. 14, lines 7-13); wherein the polynucleotide comprises at least one tumor binding domain (i.e. a tumor binding protein, such as an antibody or part of an antibody) which binds with a tumor cell-associated surface molecule that is expressed on one cell type (here an antibody to erb-2, known in the are to be expressed on breast tumor cells; see paragraph bridging p. 7-8); and wherein the vector can be used for *in vivo* delivery of polynucleotide/product of interest (e.g. p. 2, second paragraph). Anderson teaches that the vector is useful for treating cancer (see page 20, last paragraph).

Anderson also teaches that the tumor interacting protein can be expressed as a fusion protein to a product of interest (here, the targeting polypeptide expressed as a fusion protein with specific envelope proteins, such as SEQ ID NOS: 1-5 (e.g., see last paragraph, p.3 through first paragraph, p. 7); and that the envelope proteins includes a secretory signal or "leader" sequence, thus making the fusion protein a secretory protein (i.e. secreted) (see paragraph bridging p. 6-7) which would necessarily be secreted from a first cell and target an appropriate second cell.

Anderson does not specifically teach a vector that binds to a trophoblast cell surface antigen, or that the trophoblast cell surface antigen to which the vector binds is 5T4.

Myers teaches the isolation of a cDNA encoding 5T4 Oncofetal Trophoblast Glycoprotein, and indicates that 5T4 (identified by a monoclonal antibody) has been shown to be "strongly expressed on fetal trophoblast membranes, but absent from most normal non-pregnant tissues with a few epithelia [being] weakly positive" and "is expressed by a wide variety of transformed embryonic and carcinoma-derived cell lines and many different human carcinomas." (See p. 9319, paragraph bridging columns 1 and 2), thereby indicating that the 5T4 antigen is preferentially expressed on cancer cells.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the vector taught by Anderson with a substituted tumor interacting protein, wherein the substituted tumor interacting protein is the antibody (or part thereof) that specifically interacts with 5T4 taught by Myers, to create the vector of the instant claims with a reasonable expectation of success. Furthermore, Myers indicates that 5T4 antigen is preferentially expressed in cancer cells, thus it would have been prima facie obvious to one of ordinary skill in the art to modify the vector of Anderson to target cancer cells expressing the 5T4 antigen taught by Myers.

The motivation to combine the references to create claimed invention is provided by Anderson, who teaches "retroviruses can be made 'targetable' to a specific type of cell if a portion of the receptor binding region is modified such that the receptor binding region includes a polypeptide which binds to a ligand or receptor of a target cell" and mentions many different

specific examples (see middle of p. 7 through the end of p. 8) including "antibodies and fragments thereof, including single chain antibodies" (see paragraph bridging p. 7-8). Furthermore, Myers indicates that the 5T4 antigen is preferentially expressed in cancer cells, which would have motivated one of skill in the art to target cancer cells by targeting the 5T4 antigen.

1. Claims 75, 83, 84, 88, and 96, 97 and 101-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 96/30504) in view of Myers et al. (JBC Vol. 269, No. 12: p. 9319-9324; 1994) as applied to claims 75, 83, 88 and 96; and further in view of Barber (U.S Patent 5,591,692; 1997).

Anderson teaches a retroviral vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor interacting protein is targeted to a specific tumor cell type, and delivers a therapeutic product encode by a second polynucleotide of interest to the interior of the tumor cell (e.g., see abstract; p. 1, paragraphs 1-2; p. 19, second paragraph; and paragraph bridging p. 20-21); wherein the second polynucleotide of interest encodes a cytokine such as Tumor Necrosis Factors, Interferons, and Interleukins, (p. 21, second paragraph, and p. 14, lines 7-13); wherein the polynucleotide comprises at least one tumor binding domain (i.e. a tumor binding protein, such as an antibody or part of an antibody) which binds with a tumor cell-associated surface molecule that is expressed on one cell type (here an antibody to erb-2, known in the are to be expressed on breast tumor cells; see paragraph bridging p. 7-8); and wherein the vector can be used for *in vivo* delivery of polynucleotide/product of interest (e.g. p. 2, second

paragraph). Anderson teaches that the vector is useful for treating cancer (see page 20, last paragraph).

Anderson also teaches that the tumor interacting protein can be expressed as a fusion protein to a product of interest (here, the targeting polypeptide expressed as a fusion protein with specific envelope proteins, such as SEQ ID NOS: 1-5 (e.g., see last paragraph, p.3 through first paragraph, p. 7); and that the envelope proteins includes a secretory signal or "leader" sequence, thus making the fusion protein a secretory protein (i.e. secreted) (see paragraph bridging p. 6-7) which would necessarily be secreted from a first cell and target an appropriate second cell.

Anderson does not specifically teach a vector that binds to a trophoblast cell surface antigen, or that the trophoblast cell surface antigen to which the vector binds is 5T4.

Myers teaches the isolation of a cDNA encoding 5T4 Oncofetal Trophoblast Glycoprotein, and indicates that 5T4 (identified by a monoclonal antibody) has been shown to be "strongly expressed on fetal trophoblast membranes, but absent from most normal non-pregnant tissues with a few epithelia [being] weakly positive" and "is expressed by a wide variety of transformed embryonic and carcinoma-derived cell lines and many different human carcinomas" (See p. 9319, paragraph bridging columns 1 and 2), and therefore can be used to identify and target tumors expressing 5T4.

Neither Anderson nor Myers teaches that the retroviral vector further comprises tumor specific promoter.

Barber teaches a recombinant retroviral vector which can be targeted to preselected cell lines and wherein the vector comprises tissue-specific promoters such as tumor-specific

promoters (e.g., transferring receptor or Thymidine kinase; see column 4, lines 1-10 and column 21, line 12 through column 22 line 21).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Anderson and Myers (as mentioned above) with the teachings of Barber to create the vector of the instant claims with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by Anderson, who teaches the retroviral vector may further comprise a sequence encoding a therapeutic agent under the control of a suitable promoter (see paragraph bridging pages 13 and 14 and p. 15, second paragraph), and can be used to treat tumors (see paragraph bridging p. 20-21), thus indicating that expression of the therapeutic agent in tumor cells would be desirable.

Response to Arguments

2. Applicant's arguments filed 6/3/03 have been fully considered but they are not persuasive.

3. Regarding the rejection of claims under 35 USC 103 in view of Anderson and Myers, Applicants argue that Anderson doe not teach an operable linkage between the polynucleotide encoding the targeting polypeptide and a therapeutic protein. Applicants contend that Anderson teaches away from the such an operable linkage because in Anderson the targeting polypeptide must be expressed as a fusion product of a portion of the binding region of the viral envelope.

4. In response, it is respectfully pointed out that Anderson does not teach away from a polynucleotide encoding a targeting polypeptide in operable linkage with a therapeutic protein. Anderson teaches,

> "The polynucleotide encoding the targeting polypeptide or the plasmid containing such polynucleotide is cut at appropriate restriction enzyme sites and cloned into the first expression plasmid which also has been cut at appropriate restriction enzyme sites. The resulting expression plasmid thus includes a polynucleotide encoding the modified envelope protein. Such polynucleotide then may be cloned out of the expression plasmid and in to a retroviral plasmid vector. The resulting retroviral plasmid vector, which includes the polynucleotide encoding the modified envelope protein, and which may also include a polynucleotide encoding a heterologous protein or peptide, is transfected into an appropriate packaging cell line to form a producer cell line for generating retroviral particles including the modified envelope protein." (See p. 12, line 30 through p. 13, line 10).

Indicating that the retroviral vector can comprise a polynucleotide operably encoding the targeting peptide, the modified envelope protein and a heterologous protein, which can be a therapeutic protein.

Applicants also argue that there is no suggestion to combine the references.

In response, In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as previously mentioned, Anderson teaches a vector and method for targeting a therapeutic molecule to a cancer cell using the vector encoding a targeting peptide that targets the therapeutic molecule to cancer cells by recognizing a tumor specific antigen.

Myers teaches that 5T4 is a tumor specific antigen that is expressed by a wide variety of transformed embryonic and carcinoma-derived cell lines, and many different human carcinomas; indicating that it could be used to identify and target cancer cells. Therefore, one of skill in the art would have been motivated to modify the vector of Anderson such that it was targeted to 5T4 antigen because 5T4 was shown to be a tumor specific antigen by Myers.

1. Regarding the rejection of claims under 35 USC 103 in view of Anderson, Myers and further in view of Barber, Applicants argue that the claims are patentable over the teachings of Anderson and Myers for the reasons indicated above and that Barber does not over come the alleged deficiencies of Anderson and Myers and thus the rejection should be withdrawn.

2. In response, it is respectfully pointed out that the Applicants arguments rely solely on the alleged deficiencies of Anderson and Myers. However, as indicates above, the rejection of claims in view of Anderson and Myers has not been overcome, Therefore, the rejection of claims over Anderson in view of Myers and Barber is not withdrawn.

Conclusion

3. No claim is allowed.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
Patent Examiner
AU 1635